CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-986

ADMINISTRATIVE DOCUMENTS

INFORMATION ABOUT PATENTS RELATING TO INSULIN ASPART

The patent mentioned below is the known U.S. patent which claims Insulin Aspart and drug product containing Insulin Aspart. The patent belongs to the company Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark. The applicant of the present New Drug Application No. 20-986, Novo Nordisk Pharmaceuticals, Inc., 100 Overlook Center, Suite 200, Princeton, New Jersey 08540, is a subsidiary of Novo Nordisk A/S.

The following U.S. patent is issued:

- **U.S. Patent No.:** 5,618,913

  Expiration date: April 8, 2014

  Type of patent: drug substance and drug product

  Owner: Novo Nordisk A/S

  U.S. agent authorized to receive notice of patent certification:

  Steve T. Zelson, Esq.
  Director of Corporate Patents
  Novo Nordisk of North America, Inc.
  405 Lexington Avenue
  Suite 6400
  New York, N.Y.
  NY 10174-6401

APPEARS THIS WAY
ON ORIGINAL

DECLARATION CONCERNING U.S. PATENT NO. 5,618,913

The undersigned declares that Patent No. 5,618,913 covers the formulation, composition and/or method of use of insulin aspart. This product is the subject of NDA 20-986 for which approval is being sought.

Signed 31st day of August, 1998

Steve T. Zelson, Esq.
Director of Corporate Patents
Novo Nordisk of North America, Inc.
Lexington Avenue
Suite 6400
New York, N.Y.
NY 10174-6401

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Checklist

NDA: 20-986				
Trade Name: NovoLog™ (insulin aspart [rDNA origin] injection)				
Generic Name: ↓				
Applicant Name: Novo Nordisk Pharmaceuticals Inc.				
Division: DMEDP (HFD-510)				
Project Manager: Julie Rhee				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	X	No	
b. Is it an effectiveness supplement?	Yes		No	X
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	X	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination	Yes		No	X

bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.				
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	X
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes		No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in				

the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes		No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	
If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #:				
Investigation #2, Study #:				
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				

Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):				
Investigation #1				
Investigation #2				
Investigation #3				
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.				
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?				
Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?				
Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				
c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	
If yes, explain:				

/S/

8-12-99

Signature of PM/CSO
Date:

/S/ 8-26-99

Signature of Division Director
Date:

cc:
Original NDA
HFD-510/Division File
HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20986	**Trade Name:**	NOVOLOG
Supplement Number:		**Generic Name:**	INSULIN ASPART INJECTION (RDNA ORIGIN)
Supplement Type:		**Dosage Form:**	Injectable; Subcutaneous
Regulatory Action:	~~PN~~ AP	**Proposed Indication:**	For the treatment of patients with diabetes mellitus.

Except for 6/18 data in 6-12 (n=9) and 15-17 (n=9)

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

~~NO~~, No data ~~was~~ were submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

___NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

} NONE

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant has COMMITTED to doing them
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

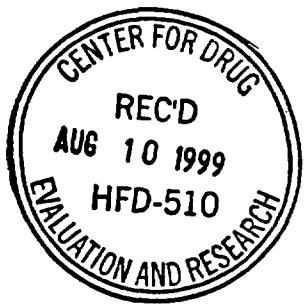
COMMENTS:
Written Request was issued on 12/14/99.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIE RHEE

/S/ 5-26-00

Signature Date

NDA AMENDMENT
Debarment Statement



Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

August 9, 1999

Solomon Sobel, M.D
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-986 **Insulin aspart (Insulin X-14) (recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to a telephone call from Ms. Julie Rhee to Robert Fischer on August 9, 1999. In that conversation, Ms. Rhee requested that we send a new debarment statement. Please find a new debarment statement attached.

If you have any questions regarding this amendment, please contact Robert Fischer, Asst. Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

APPEARS THIS WAY
ON ORIGINAL

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1); 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE Barry Reit, Ph. D., Vice President	DATE August 9, 1999
ADDRESS *(Street, City, State, and ZIP Code)* 100 Overlook Center, Suite 200, Princeton, NJ 08540-7810		Telephone Number (609)- 987- 5800

Debarment Statement

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, Novo Nordisk Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Barry Reiff, PhD
Vice President
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Debarment Statement

called 8/9
+ asked to
resubmit.

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, to the best of its knowledge, Novo Nordisk Pharmaceuticals Inc. did not use in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this submission.

Maria Ellyett for Barry Reit

Barry Reit, PhD
Vice President
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Memorandum

Date: 9/12/99

/S/

From: Saul Malozowski
Acting Medical Team Leader

Subject: NovoLog (NDA 20986). Amendment to Team leader recommendations

To: Solomon Sobel
Division Director, DMEDP

/S/ 9/12/99

In the time elapsed since my previous memo some relevant information has emerged that needs to be addressed on the record. These issues will be covered in this memo.

1) Preclinical studies indicate that NovoLog induces mammary tumors in rodents when compared to regular insulin. The studies performed by this sponsor are more extensive that any previous studies for other insulin analogs. As a result, we cannot really state that ——— , we can only state that in the past, this was not properly assessed. No signal of increased mammary signal was seen in the pivotal studies. These studies were, however, very short in duration and in young women; these are not as prone to develop mammary tumors as older females are. The label has been changed in this section to reflect these findings in rodents. Whether these findings may have any clinical significance remains unknown.
2) Both hypo and hyperglycemia are associated with embryonic and fetal malformations. Preclinical studies indicate that this product induces those in rats. Therefore, this will be addressed in the label too. It is important to stress again that the studies performed by this sponsor are more extensive that any previous studies for other insulin analogs. As a result, we cannot really state that ——— , we can only state that in the past, this was not properly assessed.
3) [ ]
4) Finally, the inspection of diverse centers has established that one of the sites was not up to standards and it was recommended that data from this location be eliminated from the analysis. This site was inspected by the Agency as a result of the sponsor's forthcoming attitude informing us a priori of these deficiencies. The medical and statistical reviews analyzed all the database with and without information from this site. The results of both analyses were similar, and it was concluded that data from this site did not alter the conclusions reached. Data from this site, however, are excluded in the label. As in most NDAs, inspection of all other sites unveiled minor deficiencies that did not change the main reviewers' recommendations.

cc: Orig NDA
HFD-510/Div File
HFD-510/Malozowski
HFD-102/Jenkins

Philip Raskin, M.D.
University of Texas
Southwestern Medical Center at Dallas
5323 Harry Hines Blvd., Room G5.238
Dallas, Texas 75235-8858

MAY 12 1999

Dear Dr. Raskin:

Between January 14 and February 5, 1999, Ms. Kelly J. Pegg, from the Food and Drug Administration (FDA), inspected your conduct of a clinical study (Protocol Nos. ANA/DCD/036/USA and ANA/DCD/037/USA) of the investigational drug human insulin analogue X-14. You conducted this study for Novo Nordisk Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we found some deviations from Federal regulations and/or good clinical investigational practices. These deviations were detailed on the Form FDA 483 and discussed with you at the close of the inspection. The deviations from the study protocol are:

1. Subjects ———— were admitted to the study with body mass indexes greater than 35 prior to IRB approval of the protocol amendments (21 CFR 312.30(a)(2)).

2. The medical records available during the inspection failed to support the diabetic history/insulin treatment dates reported for subjects ———— in their respective case report forms (21 CFR 312.62(b)).

The explanations you provided during the discussion are part of the inspection records. We expect that corrective measures will be instituted accordingly.

We appreciate the cooperation shown Ms. Pegg during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practice Branch I, Room 125
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
144	/S/	5/12/99			
347	/S/	5/12/99			

FILE
CC:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Andrew J. Green, M.D.
Midwestern Endocrinology PA
10550 Quivira Road, Suite 270
Overland Park, Kansas 66215

MAY 12 1999

Dear Dr. Green:

Between January 11-19, 1999, Ms. Linda R. Kuchenthal, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (Protocol No. ANA/DCD/036/USA of the investigational drug human insulin analogue X14, performed for Novo Nordisk Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and of the documents submitted with that report, we find some deviations from Federal regulations and/or good clinical investigational practices which were detailed on the Form FDA 483 and discussed with you at the close of the inspection. The deviations included failure to report: 1) all the adverse events for subject —— 2) concomitant medications for subjects —————— and 3) correct ECG information for subject —— Your explanations in your letter dated January 27, 1999 are acceptable and will be included as a permanent part of the inspection records. We expect, as you stated, that corrective measures will be instituted accordingly.

We appreciate the cooperation shown Ms. Kuchenthal during the inspection.

Sincerely yours,

/S/ for BLB

Bette L. Barton, Ph.D., M.D.
Chief
Good Clinical Practice Branch I
Division of Scientific
Investigations
Office of Medical Policy
Center for Drug Evaluation
and Research Room 125
7520 Standish Place
Rockville, Maryland 20855

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

20-780

ORIGINAL

FEB 19 1999

Sherwyn L. Schwarts, M.D.
Diabetes & Glandular Disease
Clinic P.A.
8042 Wurzbach Road Suite 420
San Antonio, Texas 78229

Dear Dr. Schwarts:

Between January 11-14, 1999, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (Protocol No. ANA/DCD/036/USA of the investigational drug human insulin anlogue X14, performed for Novo Nordisk Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and of the documents submitted with that report, we conclude that you did adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Mr. Martinez during the inspection.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

APPEARS THIS WAY
ON ORIGINAL

September 14, 1999
Memorandum
To: the file NDA 20-986 Novolog
From: Solomon Sobel M.D. Director, Divison of Metabolic and Endocrine Drug Products
Subject: Approvability of NDA, 9/14/99

This insulin [NovoLog --insulin aspart(rDNA origin) is the second insulin analog that our Division has reviewed. It is a rapid acting insulin similar in its time course of action to the previously approved analog,lispro.

The efficacy studies performed in type 1 diabetics (two studies) and in type 2 diabetics (one study) give substantial evidence that this insulin is not inferior to regular human insulin in its efficacy in respect to HbA1c after 6 months of treatment.

Some issues in respect to safety deserve comment.
Since this is a xenobiotic in respect to its molecular structure (amino-acid sequence) we are especially interested in its immunogenicity. The data indicate that there is no clear finding of increased production of specific antibodies against IAsp. Antibody levels were determined at baseline and at month 6 in all 3 pivotal studies. Those patients treated with IAsp showed a statistically significant increased percentage of patients with cross-reactive insulin antibodies. This increase was not seen in those patients treated with human insulin.

However, increases to specific antibodies to IAsp or human insulin was not seen in the IAsp treated patients. Neither was this seen in human insulin treated patients.
There was a finding of a trend towards an increase in cross-reactive antibodies with the increase in basal insulin (which was NPH human insulin).
We have addressed these findings in the labeling.

With respect to the pre-clinical findings the following requires comment. "The incidence of benign and malignant mammary gland tumors in female rats was increased with all doses of Novolog compared to vehicle controls. The tumor incidence with Novolog was slightly higher than with regular human insulin. The relationship of these findings to humans is unclear. Novolog was not genotoxic..." (in five in vitro tests).
We do not believe that these findings are of sufficient concern to withold approval but they will be mentioned in the labeling.

Another safety concern was in respect to hypoglycemic events. There was no statistical difference in this parameter between IAsp and human insulin. As expected there were some differences in respcct to the time of day of occurrence. For example,IAsp treated patients had fewer nocturnal events.

The reason that we cannot move to an approval at this time is that the inspection of the manufacturing facility revealed deficiencies which are of sufficient magnitude to warrant a delay in approval until they are corrected.
Also, we are in the final negotiations on the labeling and will submit our recommended labeling to the sponsor with the approvable letter. Also, we will submit our recommended text for the informational material for the patient, shortly.

Conclusion:
The Division recommends that an approvable letter be sent.
-Solomon Sobel

/S/

cc: Orig NDA 20-986
HFD-510/Div File
HFD-510/Malozowski/Koller

Memorandum

Date: 8/23/99

/S/

From: Saul Malozowski
Acting Medical Team Leader

Subject: NovoLog (NDA 20986). Team leader recommendations

To: Solomon Sobel
Division Director, DMEDP

In assessing the information reviewed by all disciplines regarding this insulin analog all the data presented by the sponsor indicates that NovoLog has shown proof of "non-inferiority" to regular insulin in its ability to induce long-term glucose control. In contrast to regular insulin, NovoLog presents a unique property: It is more rapidly absorbed. This property allows patients to receive this insulin analog at mealtime. Therefore, although this product is not superior to the used comparator product, it provides a ease of use advantage to regular insulin that needs to be given half an hour before meals.

The toxicological review has shown that rats develop mammary tumors when receiving insulins. The difference between NovoLog and regular insulin was not statistically significant for a NovoLog dose >30 times of the human dose. These growth promoting findings for insulins should be stressed, because NovoLog has structural and physiological similarities to insulin like growth factor moieties, that in numerous in vitro and in vivo studies both in animals and in human models have been shown to induce-promote growth independently of their glucose lowering properties. Although the pivotal studies in humans did not show any signs of increased tumorogenesis in subjects receiving NovoLog, they were not powered to address this issue. The clinical significance of the animal findings remains uncertain.

In the clinical studies the medical reviewer has stressed that patients receiving NovoLog received more insulin (1-3 units more) than subjects on regular insulin. This observation is correct. It is also valid to state that this resulted in a significantly better control as seen by HBA1C values (~0.13%) in the NovoLog treated patients. The clinical significance of the increased dose of insulin as well as the statistically improvements in HbA1C in subjects receiving NovoLog is dubious. These differences were probably the result of the protocol design that stated for all three pivotal studies that *" Subjects receiving" NovoLog" were advised that an increase in their basal insulin requirements might occur during the treatment with" NovoLog.* Because the Sponsor is not claiming superiority, any further discussion on this issue appears not to be relevant.

It is difficult to reach a conclusion, however, on NovoLog effects on glycemia because these effects were determined using glucometers, devices that lack accuracy to establish any relevant efficacy claim.

As with any insulin product, hypoglycemia occurred during the study. The methodologies used to assess these episodes is properly questioned in the medical review. Despite the shortcomings of the studies to properly assess these events, all the information provided appears to indicate that patients receiving NovoLog are not at increased risk of developing hypoglycemia that those receiving regular insulin.

Outliers for alkaline phosphatase, BUN, bilirubin, and ASAT levels as well as MCV were observed in some of the studies. None of these changes necessitated study discontinuation. The clinical significance of these abnormalities is not clear, but they appear not to pose an undue risk to subjects receiving NovoLog.

All other severe adverse events, including death, were similar among treatment arms and no information is available that suggest that this product possess more risk that regular insulin

Insulin antibodies increased significantly from baseline in all three pivotal studies in subjects receiving regular insulin at months three and six. This was not observed with NovoLog. Antibody levels decreased significantly from 3 to 12 months and returned to baseline levels. The clinical significance of these changes is unknown.

Conclusion:
I recommend approval of this product pending modifications to the submitted label in order to properly reflect the findings of the studies.

NDA 20-986 May 2, 2000

DRUG: Insulin Aspart (Insulin X-14, [redacted]
INDICATION: Treatment of Type 1 and Type 2 diabetes

TEAM LEADER MEMO TO FILE REGARDING
PRECLINICAL PHARMACOLOGY/TOXICOLOGY LABELING ISSUES FOR SPONSOR SUBMISSION OF April 28, 2000
FOR NDA 20-986 (Insulin Aspart, Insulin X-14, NovoLog™)

4/28/00 Sponsor label proposal for carcinogenicity section:

Standard 2 year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog™. In 52 week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog™ at 10, 50 and 200 U/kg/day. [redacted]. The incidence of mammary tumors for NovoLog™ was not significantly different than regular human insulin. The relevance of these findings to humans is not known.

FDA RESPONSE MARKED COPY:

Standard 2 year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog™. In 52 week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog™ at 10, 50 and 200 U/kg/day **(approximately 2, 8 and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively)**. At a dose of 200 U/kg/day [redacted]. The relevance of these findings to humans is not known.

JUSTIFICATION: The executive CAC indicated that the significant increase in mammary tumors relative to untreated to control should be indicated in the label. Multiples of all doses tested were included to allow the reader to determine the relative exposure for the dose at which the findings occurred and also includes information for doses where the findings did not occur. The inclusion of the insulin findings provides perspective as to the potential relevance of the findings.

"CLEAN" COPY OF FDA PROPOSAL.

Standard 2 year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog™. In 52 week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog™ at 10, 50 and 200 U/kg/day (approximately 2, 8 and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog™

[ ]

. The relevance of these findings to humans is not known.

PREGNANCY CATEGORY COMMENTS:

The sponsor proposes adding the section which we had previously deleted as "class labeling". I hesitate to call this a class label because our recommendations may vary for other insulin analogs and may not be appropriate for newer analogs if the findings turn out to be significantly different from insulin. However, the toxicology findings with NovoLog™ appear to be similar to regular human insulin, which was tested in the same experiments as NovoLog™. If the goal is to have the best glucose control and this product is working better than regular human insulin in a particular patient, pharmacology sees no reason not to include these statements in the label. This is consistent with the Lantus™ and Humalog® labels. Reproductive studies with Lantus™ had similar findings as NovoLog™.

Pharmacology notes that there were animal findings in the reproductive toxicology studies with NovoLog™ which were interpreted by the Reproductive Toxicology committee to necessitate that NovoLog™ be classified as Pregnancy Category C. However, pharmacology also notes that these findings occurred at 32 times the human recommended dose based on body surface area and that there were no such findings at approximately 8 times the human dose. From a nonclinical standpoint, this does not appear to pose a risk for human use, but appropriate cautionary labeling should be included as outlined in the CFR. This would include the first statement

[ ]

Pharmacology views the later statements as recommendations for clinical use and thus defers to the Medical team to determine whether these statements should be modified or removed.

/S/ 5/2/02

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader DMEDP
cc: NDA Arch
HFD510
HFD510/Steigerwalt/Antonipillai/Koller/JRhee
Review Code: AP (pending labeling revisions)
Filename: 20986:52lbl.doc

NDA 20-986 July 23, 1999

DRUG: Insulin Aspart (Insulin X-14, ————)
INDICATION: Treatment of Type 1 and Type 2 diabetes

TEAM LEADER MEMO TO FILE REGARDING PRECLINICAL PHARMACOLOGY/TOXICOLOGY ISSUES FOR NDA 20-986 (Insulin Aspart, Insulin X-14, ————)

The following statements are based upon Dr. Antonipillai's pharmacology review of NDA 20-986.

Insulin X-14 is a recombinant human insulin with the modification of the natural human insulin molecule in which proline at the β28 position has been replaced by aspartic acid. This is designed as a rapidly acting insulin.

In general, the preclinical studies performed with this agent indicated that the toxicological findings with X-14 are similar to human insulin and in most cases, are likely due to the expected hypoglycemia at high dose levels.

The carcinogenicity assessment of compounds such as modified insulins is problematic. In general, the standard 2-year bioassay approach is not appropriate for biotechnology products. However, in some cases, particularly where mitogenic or potential carcinogenic effects may be suspected, some kind of approach is necessary to provide information regarding carcinogenic potential. General approaches are outlined in the ICH S6 document for biotechnology products. There are no 2-year bioassay data available for insulin. Literature would suggest that there could be, at minimum, a finding of increased incidence of mammary tumors with chronic high dose treatment in rats. The mechanism for this is not clear, but may be related to cross reactivity with the IGF-I receptor. Current evidence suggests that there is no association of increased cancer in human populations treated therapeutically with exogenous insulin.

The dilemma for carcinogenicity testing of insulin analogs raises three key questions:
1. How different does an insulin analog have to be from human insulin to spur extensive testing for carcinogenicity potential?
2. Since it is likely that insulin would exhibit some carcinogenic potential in a standard bioassay yet has not been tested as such, what is to be done with a positive finding with an analog which might have no real different potential than insulin?
3. How relevant to clinical use are tumor findings in animals treated with high doses of insulin analogs?

The sponsor chose a logical, multifaceted approach to the carcinogenicity assessment. The approach was as follows:
1. Standard genetic toxicology testing.
2. Comparative binding studies of insulin analogs and insulin to both insulin and IGF-I receptors.
3. Assessment in mitogenicity assays (MCF-7 cells) compared to human insulin.
4. 1-year toxicology studies in rats with a human insulin comparator arm.

Overall, these studies suggested that the potential for a carcinogenic response to X-14 is similar to, but possibly slightly higher than that of regular human insulin. The findings of these studies are briefly summarized as follows:

1. Genotoxicity: X-14 was not mutagenic or clastogenic in the Ames bacterial mutagenesis assay, the mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice and *ex vivo* UDA test in rat liver hepatocytes.
2. Receptor affinity: Relative affinity for insulin vs IGF-I receptors suggested that both human insulin and insulin X-14 have low affinity for the IGF-I receptor and similar affinity for the insulin receptor.
3. Mitogenicity: The mitogenicity test findings in MCF-7 cells were inconclusive. There was a great deal of variability between experiments for relative mitogenicity comparisons between insulin, insulin X-14 and [redacted] The relative mitogenicity compared to human insulin ranged from 0-84 for insulin X-14 and 8-404 for [redacted] Although the sponsor concluded that this suggested that insulin X-14 showed similar mitogenicity to human insulin, the lack of reproducibility here casts some doubt on the utility of the data presented from these experiments. Perhaps alternative cell lines may provide more reproducible data. The pharmacology reviewer recommends that reference to these studies in the label that was initially proposed by the sponsor be removed. The pharmacology team leader agrees with her assessment based on the fact that these findings are inconclusive.
4. Tumorigenesis: Two 1-year rat studies were presented which provide comparisons between insulin, insulin X-14 and [redacted] These varied in dose regimen (once a day vs twice a day). The primary tumor finding in one-year studies with all three agents was mammary tumors. This is extensively discussed in the pharmacology review and the team leader refers the reader to this section in Dr. Antonipillai's review. In correlation with its increased affinity for the IGF-I receptor, [redacted] caused a statistically significant increase in mammary tumors when compared to controls. Both insulin and insulin X-14 also caused an increase in mammary tumors compared to controls. It appeared that this effect was slightly higher for insulin X-14 compared to human insulin. There was, however, no statistically significant difference in the occurrence of mammary tumors detected between human insulin and insulin X-14 ($p = 0.062$). It is emphasized that to this reviewer's knowledge, there is no epidemiological association of insulin treatment with increased cancer risk after many years of use.

In the initial proposed labeling, the sponsor indicates that findings in the one-year studies were similar to insulin, without mentioning the mammary tumor findings. Since the incidence of mammary tumors was slightly higher with X-14, the reviewer suggested that a brief discussion of the tumor findings in the label was appropriate. The team leader agrees with this assessment and our recommendations for labeling reflect this conclusion. I do note, however, that given the fact that there was not a statistical difference between insulin X-14 and insulin and the finding occurred at a relatively high multiple of human exposure (~32 times the human exposure), I do not believe that insulin X14 poses a carcinogenic risk greater than insulin at therapeutic doses.

The pharmacology team leader recommends that this application should be approved (AP) from a pharm/tox standpoint pending appropriate modifications to the label.

/S/ 7/23/99

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Antonipillai/Koller/JRhee
Review Code: AP (pending labeling revisions)
Filename:

APPEARS THIS WAY
ON ORIGINAL

Memorandum

Date June 6, 2000

From Steven R. Koepke, /S/
Deputy Director, Division of New Drug Chemistry II,
Office of New Drug Chemistry

Subject NDA 20-986
Novolog insulin aspart injection [rDNA origin]
Novo Nordisk Pharmaceuticals Inc.

Novolog is a recombinant insulin analogue, insulin aspart. The primary structure of the protein is identical to that of human insulin with the exception of a proline to aspartic acid mutation at the — position. This substitution results in a more rapid action of the drug and a decrease in hexamer formation. The product a buffered and preserved aqueous solution with a potency of 100 U/mL. Novolog is equipotent to human insulin on a molar basis. The drug product will be marketed in prefilled 3 mL syringes, 10mL vials and —— 3.0mL cartridges for use in refillable or disposable insulin pens. These are same as the presentations for the approved Novolin insulin [rDNA origin] product. These products are identical in nature with the exception of the substitution of the aspartic acid at the — position.

Overall CMC recommendation: There are no outstanding CMC issues as of CMC review #3. The last CMC issue was an acceptable inspection of the facilities and has been accomplished. The application is recommended for approval from CMC.

Environmental assessment: The firm has claimed categorical exclusion in the original application and this was found acceptable Feb. 4, 1999.

Facility Inspections: Acceptable 12/15/99

Tradename: Acceptable LNC 4/28/99 but OPDRA has concerns 6/6/00 with similarity to Novolin.

Labeling: Acceptable overall from CMC, but we recommend that the established name be made more prominent on the vial, cartons, cartridges and prefilled syringes at the next printing. While the established name on the labels appears to be exactly half in font size versus the tradename, the prominence is lessened by differences in font type and/or bolding of the tradename. The package insert "How Supplied" section contains only the 3 mL cartidges and 10 mL vials. The additional packaging presentations should be added to this section.

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
1161	510	NovoLog	
ATTENTION:	William K. Berlin		

A. Look-alike/Sound-alike

	Potential for confusion:
Novolin	XXX Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

____ Satisfactory
____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 4/28/99

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 20986/000**
Priority: **1S** Org Code: **510**
Stamp: **16-SEP-1998** Regulatory Due: **07-JUN-2000**
Action Goal: District Goal: **18-JUL-1999**
Applicant: **NOVO NORDISK PHARM**
100 OVERLOOK CENTER STE 200
PRINCETON, NJ 085407810
Brand Name: **NOVOLOG**
Established Name:
Generic Name: **INSULIN ASPART INJECTION (RDNA ORIGIN)**
Dosage Form: **INJ (INJECTION)**
Strength: **100 U/ML**

FDA Contacts: **H. RHEE** **(HFD-510)** **301-827-6424** **, Project Manager**
ID = 121714 **, Review Chemist**
S. MOORE **(HFD-510)** **301-827-6430** **, Team Leader**

Overall Recommendation:

ACCEPTABLE on 15-DEC-1999 by S. FERGUSON (HFD-324) 301-827-0062
WITHHOLD on 14-SEP-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: **9610095**
NOVO NORDISK A/S

BAGSVAERD, , DA

DMF No:
AADA No:

Profile: **CFN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
FINISHED DOSAGE MANUFACTURER

Establishment: **9610699**
NOVO NORDISK A/S
HALLAS ALLE
KALUNDBORG 4400, , DA

DMF No:
AADA No:

Profile: **CFN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-DEC-1999**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9613244**
NOVO NORDISK A/S
BERNNUM PARK, DK-3400
HILLEROED, , DA

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

APPEARS THIS WAY ON ORIGINAL